

The Relative Contributions of Birth Weight, Weight Change, and Current Weight to Insulin Resistance in Contemporary 5-Year-Olds

The EarlyBird Study

Terence J. Wilkin,¹ Bradley S. Metcalf,¹ Michael J. Murphy,² Joanne Kirkby,¹ Alison N. Jeffery,¹ and Linda D. Voss¹

For more than a decade, the fetal programming hypothesis has taught that insulin resistance and its associated metabolic disturbances result from poor gestational environment, for which low birth weight is a surrogate. Low birth weight, however, is now uncommon in industrialized societies. We have investigated the relevance of birth weight, “catch-up” weight, and current weight to insulin resistance in 300 contemporary British children. Insulin resistance at 5 years was not related to birth weight but was correlated with current weight and weight catch-up in both sexes, more strongly so in girls ($r = 0.33$, $P < 0.001$ vs. $r = 0.18$, $P = 0.03$), who were intrinsically more insulin-resistant than boys. Weight change merely co-correlated with current weight ($r = 0.67$, $P < 0.01$ in both sexes) and did not improve on the prediction of insulin resistance. Most important, insulin resistance at 5 years was the same in children of heavier birth weight, whose weight SD score had not changed, as in those of lighter birth weight, matched for current weight, who had experienced so-called catch-up (boys 0.89 and 0.88 units, respectively, $P = 0.96$; girls 1.26 and 1.13 units, $P = 0.41$). Insulin resistance in contemporary children seems to be a function of excess current weight rather than of low birth weight or change in weight. *Diabetes* 51:3468–3472, 2002

Type 2 diabetes is the outcome of a process—it is not the process itself. The process is one of insulin resistance, in which high levels of circulating insulin reflect the response of the β -cells to a rising blood glucose. Type 2 diabetes emerges when the β -cells are no longer able to compensate (1), whereas the accompanying hyperinsulinemia is independently associated with other metabolic disturbances collectively referred to as the metabolic syndrome (2). These disturbances together account for much of the cardiovascular

From the ¹Department of Medicine, The Peninsula Medical School, Plymouth Campus, U.K.; and the ²Department Clinical Chemistry, Derriford Hospital, Plymouth, U.K.

Address correspondence and reprint requests to Prof. Terence J. Wilkin, MD, University Medicine, Level 7, Derriford Hospital, Plymouth PL6 8DH, U.K. E-mail: t.wilkin@plymouth.ac.uk.

Received for publication 12 June 2002 and accepted in revised form 29 August 2002.

HOMA-IR, homeostasis model assessment for insulin resistance; SDS, standard deviation score.

morbidity of the industrialized world (3,4) and tend not to occur in the absence of insulin resistance.

Of the three hypotheses advanced to explain insulin resistance (“thrifty genotype” [5], “fetal origins” [6], and “fetal insulin” [7]), the second, or “Barker” hypothesis, has enjoyed the widest exposure. It sees low birth weight as a surrogate for poor gestational environment and interprets the (inverse) correlation between birth weight and insulin resistance later in life as the result of “fetal programming.” The strongest predictor of future cardiovascular disease reportedly combines low ponderal index (kg/m^3) at birth with rapid weight gain thereafter—so-called “catch-up” (8–10).

The fetal programming hypothesis was originally formulated on data from metabolic studies conducted in aging males who were born before the second world war. Many of them were born into circumstances of relative poverty, in which low birth weight is more common. However, as Lucas et al. (11) have pointed out, birth weight is likely to be as valid a surrogate for nutritional circumstances after birth as before birth because birth weight and subsequent weight correlate. It may therefore be as logical to ascribe metabolic disturbance later in life to events after birth as to prenatal programming. Furthermore, low birth weight at term ($<2,500$ g) is nowadays rare in industrialized societies (12), and the privations that prevailed 80 years ago no longer apply to contemporary pregnancies. In this study, we tested the hypothesis in a cohort of young U.K. children that insulin resistance can nowadays be best accounted for by current weight (overfeeding/underactivity) rather than by birth weight (gestational environment/insulin resistance genes) or catch-up weight.

RESEARCH DESIGN AND METHODS

This report analyses two data sets. The first, based on the Plymouth NHS Child Registry, is used to provide annualized means and trends in weight at birth and at 5 years for all children born after 37 weeks’ gestation (term) in Plymouth during the period 1988–1998. The second is a subset, the EarlyBird cohort (1995 birth cohort).

Recruitment. EarlyBird is a nonintervention prospective cohort study monitoring 300 healthy children from school entry at the age of 4/5 years to the age of 16. The protocol complies with the Declaration of Helsinki, and Local Research Ethics Committee approval was obtained early in 1999. All 71 Plymouth primary schools were identified, and their directors were asked for agreement to participate in the study. Fifty-three agreed, from which 28 were randomly selected from four groups stratified socioeconomically according to the proportion of pupils in the school entitled to free school meals. Registra-

tion for the study was invited during parent induction meetings for school entry, and the children and their parents were asked for assent and consent, respectively. Parents who expressed interest were followed up with a full written explanation, and 300 trios (child and parents) have become the EarlyBird cohort. Every effort is made to minimize attrition by close family support, events, newsletters, and so forth. Fewer than 3% of the children were lost during the 18-month recruitment period.

Measures. The EarlyBird children are reviewed every 6 months in the Department of Child Health at Derriford Hospital. This report is confined to baseline measures at school entry on the entire cohort of 307 children: 170 boys and 137 girls (mean age 4.9 SD \pm 0.29 years). All were ethnically white Caucasian.

Fasting insulin (insulin-specific monoclonal antibody; Immulite DPC, Los Angeles, CA), glucose, insulin resistance (homeostasis model assessment for insulin resistance [HOMA-IR]) (13,14), height, and weight were measured. BMI was derived from the ratio kg/m². Subcutaneous fat was measured by skinfold calipers at five sites: triceps, biceps, subscapular, paraumbilical, and suprailiac. Birth weights were obtained from the Plymouth Child Registry, and all premature births (gestation <37 weeks) were excluded from the analyses of both data sets. Weight catch-up was calculated by weight standard deviation score (SDS) at 5 years minus birth weight SDS.

Statistics. SPSS for Windows (v. 9.0) was used for statistical analysis. Regression analysis was used to study the trends in birth weight and weight at 5 years. Weight was distributed normally, and insulin resistance, when log-transformed, was close to normal (means for insulin resistance are reported in real values for ease of interpretation). ANOVA and ANCOVA were used for the comparison of group means. The inclusion of a covariate in the ANCOVA model removes its contribution to the outcome variable, leaving adjusted group means. Product moment correlations were used to study associations between variables. Partial correlation was used to measure the association that remained between insulin resistance and birth weight after controlling for the collinearity of weight at 5 years. Regression model building was carried out so that the predictive effect of adding variables, one at a time, could be measured. The change in r^2 expressed the effect of each additional variable in the prediction of insulin resistance.

RESULTS

1988–1998 data set. Of the 43,971 pregnancies in this data set, 42,854 went to term (>37 weeks), and of the offspring, 2.5% weighed <2,500 g at birth. There was a statistically significant, though small, upward trend in birth weight at term during the 11 years (1988–1998) of 0.008 SDS (2.7 g) per year. During the same period, however, there was a substantially greater upward trend in BMI at 5 years by an average of 0.052 SDS or 0.089 kg/m² ($P < 0.001$) per year (boys = 0.048 SDS or 0.071 kg/m² per year, $P < 0.001$; girls = 0.056 SDS or 0.109 kg/m² per year, $P < 0.001$). The trend in BMI SDS during the 11-year period was not significantly different between boys and girls ($P = 0.39$).

EarlyBird cohort (1995 birth cohort).

Birth weight, weight change, and current weight. Of the 307 births, 22 were premature (<37 weeks), and of the remaining 285, blood samples were unobtainable at baseline in 5. One child was nonfasting. Four of the remaining 279 children (1.4%) who were available for analysis (boys $n = 154$; girls $n = 125$) weighed <2,500 g at birth. There was no difference in mean weight at birth between boys and girls. At 5 years, boys and girls were not significantly different for height or weight, but BMI was significantly greater in girls (16.5 vs. 16.0 kg/m²; $P < 0.01$). There was no significant difference in waist circumference, but hip circumference was significantly greater in girls (59.2 vs. 57.5 cm; $P < 0.01$) and the girls carried significantly more subcutaneous fat than boys (sum of skinfolds 4.71 vs. 3.85 cm; $P < 0.001$).

There was a correlation between weight at 5 years and birth weight (boys $r = 0.41$, $P < 0.001$; girls $r = 0.22$, $P = 0.01$). There were (predictably) yet stronger correlations

TABLE 1

Effects of adding birth weight and weight change to the prediction model for insulin resistance once current weight has been accounted for

Model	df	r	r^2	r^2 change	r^2 change P value
Boys					
Weight SDS at 5 years	152	0.18	0.033	0.033	0.03
Weight SDS at 5 years + birth weight	151	0.21	0.045	0.012	0.18
Weight SDS at 5 years + weight SDS change	151	0.21	0.045	0.012	0.18
Girls					
Weight SDS at 5 years	123	0.33	0.111	0.111	<0.001
Weight SDS at 5 years + birth weight	122	0.35	0.121	0.011	0.22
Weight SDS at 5 years + weight SDS change	122	0.35	0.121	0.011	0.22

The effect of adding birth weight SDS to the model containing weight SDS at 5 years is identical to that of adding weight change. This is because weight change is equal to weight SDS at 5 years minus birth weight SDS.

between weight at 5 years and change in weight SDS since birth (up or down) in both sexes (boys $r = 0.67$, $P < 0.001$; girls $r = 0.67$, $P < 0.001$) and between birth weight and the number of weight SDS crossed by 5 years of age (boys $r = -0.40$, $P < 0.001$; girls $r = -0.59$, $P < 0.001$).

Body mass and insulin resistance. There was no relationship in either sex between birth weight and insulin resistance at 5 years, even when controlling for weight at 5 (boys $r = -0.11$, $P = 0.18$; girls $r = -0.11$, $P = 0.23$). There was a modest correlation between insulin resistance and weight at 5 years in the girls ($r = 0.33$, $P < 0.001$), less so in the boys ($r = 0.18$, $P = 0.03$). Substitution of BMI for weight did not improve the correlations with insulin resistance.

The girls at 5 years were significantly more insulin resistant than the boys (1.09 vs. 0.80 units or 136%; $P < 0.001$), even when corrected for current weight, height, waist circumference, hip circumference, and subcutaneous fat. The inclusion of all six anthropometric variables together as covariates in the model still left the girls substantially more insulin resistant than the boys (0.82 vs. 1.03 or 126%; $P = 0.004$). For this reason, it was appropriate to analyze further the data from the girls and the boys separately.

Weight change and insulin resistance. There were modest correlations between insulin resistance and weight SDS crossed (up or down) since birth in boys ($r = 0.21$, $P = 0.01$) and in girls ($r = 0.30$, $P = 0.001$). However, the correlations between insulin resistance and weight change were similar to those with current weight SDS, and, in a regression analysis, neither birth weight nor weight SDS crossed since birth improved on current weight in the prediction of insulin resistance (Table 1). Indeed, as noted previously, SDS crossed since birth and current weight SDS were tightly co-correlated in both boys and girls.

On the basis of these observations, boys and girls separately were divided into a matrix of four groups according to weight SDS above or below their median at birth and at 5 years (Fig. 1). It was appropriate to use the

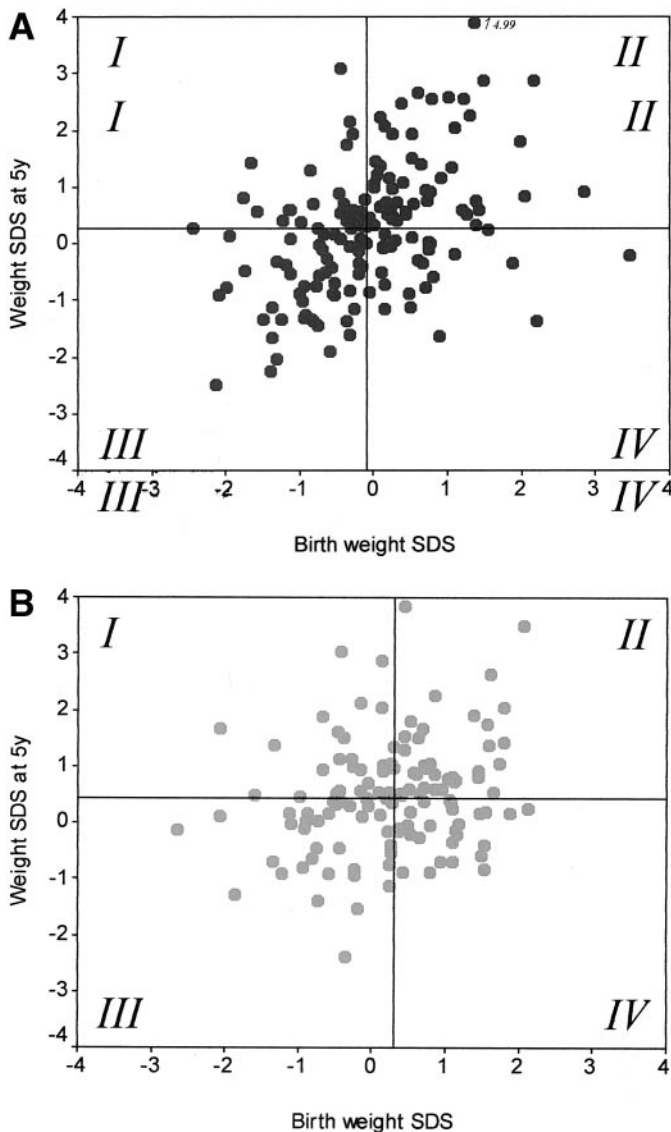


FIG. 1. Matrix of four cells identifying boys (A) and girls (B) whose weight lay variously above (high) or below (low) the median at birth and at 5 years. Cell I, low-high (catch-up); cell II, high-high; cell III, low-low; cell IV, high-low (catch-down). Mean insulin resistances for cells I and II were compared to test the catch-up hypothesis (Table 2).

medians of the cohort because their mean birth weights, particularly weight at 5 years, were slightly greater than those of the 1990 U.K. Growth Standards. The cells gener-

ated four groups of children for each sex, among them were those (low-high) who exhibited so-called catch-up. Although, as noted above, insulin resistance was higher in the heavier children, there was no difference in insulin resistance (or insulin resistance corrected for weight at 5 years) between those who had below-median birth weight and moved up the centiles to achieve a current weight above median (low-high) and those who had above-average birth weight and whose weight remained above median at 5 years (high-high; Table 2).

Insulin resistance and metabolic disturbance. Fasting glucose varied directly with insulin resistance in children of both sexes (boys $r = 0.35$, $P < 0.001$; girls $r = 0.33$, $P < 0.001$). Fasting insulin levels correlated closely (and predictably) with insulin resistance in both sexes (boys $r = 0.99$, $P < 0.001$; girls $r = 0.98$, $P < 0.001$). Fasting insulin in the children also correlated as closely as did insulin resistance with the anthropometric and metabolic variables measured (data not shown).

DISCUSSION

This study makes three important observations. First, there seems to be no relationship in contemporary children between birth weight and insulin resistance. Second, girls are intrinsically more insulin resistant than boys—and substantially so. We have expanded on this observation elsewhere (Murphy MJ et al., submitted for publication). Third, and of fundamental importance to the management of the problem, insulin resistance is the same in children who had relatively high birth weight and remain on their higher weight centile as in those who had lower birth weight and subsequently attain it. If low insulin resistance (high sensitivity) is the ideal for metabolic health, then the findings suggest that some of our offspring are already too heavy at birth and that encouragement to those of lower birth weight to join them is detrimental.

Although birth weight has been rising slowly during the past decade in the southwest of England, weight at 5 years has been rising faster. The trend is apparent from the 1988–1998 data set and has been reported elsewhere (15). It means that the average child is gaining excess weight early during childhood and, as a result, is moving upward across weight centiles set only 12 years ago.

We were unable to demonstrate a relationship between insulin resistance and birth weight in contemporary U.K. children, whether insulin resistance was controlled for current weight or not. Whereas we are concerned in the

TABLE 2

Comparison of mean weight at 5 years (95% CI), insulin resistance, and insulin resistance corrected for mean weight at 5 years between children whose weight caught up with those whose weight remained above the median from birth

Weight change	n	Weight at 5 years (kg)	Insulin resistance (arbitrary units)	Insulin resistance corrected for weight at 5 years
Boys				
I	25	20.5 (19.6–21.4)	0.85 (0.61–1.09)	0.89 (0.62–1.16)
II	52	22.2 (21.2–23.2)	0.90 (0.71–1.09)	0.88 (0.70–1.06)
		$P = 0.03$	$P = 0.75$	$P = 0.96$
Girls				
I	25	21.6 (20.6–22.6)	1.23 (0.95–1.52)	1.26 (1.03–1.49)
II	37	22.0 (20.8–23.2)	1.15 (0.95–1.35)	1.13 (0.94–1.32)
		$P = 0.58$	$P = 0.61$	$P = 0.41$

Boys and girls are treated separately, and the P values denote the statistical probability of nil difference for each comparison.

EarlyBird Study with insulin resistance in children rather than glucose intolerance in the elderly (Barker's original outcome measure), recent reports from rural India have shown correlations in childhood between birth weight and insulin resistance (HOMA) that we cannot (16). There are a number of possible reasons for the discrepancy. The prevalence of low birth weight (defined as <2,500 g) in the pre-World War II populations on which the "fetal origins" hypothesis was formulated was ~10% (6,17) and in the more recent studies from the Asian subcontinent as high as 30% (16). In contrast, low birth weight was uncommon (1.4%) in the contemporary U.K. cohort studied here. Some define low birth weight by the lowest decile, but proportions may prove misleading where absolute birth weight has an effect on insulin resistance and a secular change continues. It may be that low birth weight is associated with gestationally programmed insulin resistance that is no longer seen in contemporary children of higher birth weight.

Again, the attribution by Barker of low birth weight/insulin resistance and subsequent metabolic disturbance to poor gestational nutrition may have been intuitive but unduly exclusive. There are other possibilities. Hattersley and Tooke (7) have shown that genetic mutation can influence both birth weight and insulin resistance in rare individuals, although genes that are capable of exerting such an effect in a population have yet to be identified. Furthermore, birth weight is only a surrogate for gestational status. As pointed out earlier (11) and confirmed in this study, birth weight correlates with postnatal size, questioning the justification for ascribing metabolic disturbances later in life solely to gestational events. According to the fetal origins hypothesis, the secular rise in birth weight during the past half-century (as a result of presumed better gestational environment) should have been accompanied by a progressive fall in insulin resistance and improvement in glucose tolerance. Instead, the industrialized world is witnessing a rise in the incidence of type 2 diabetes associated with rising postnatal weight (18,19).

Finally, we may have investigated too few subjects (and modern birth cohorts may incorporate too few low birth weight subjects) to have revealed a relationship between birth weight and insulin resistance. However, birth weight did not improve on current weight in the prediction of insulin resistance. There also was not a correlation between birth weight and insulin resistance when controlling for current weight. Furthermore, the correlations of higher statistical significance in one sex but not in the other argue against imprecision of the measurement as a basis for error in disclosure. Power calculations indicate that at least 1,200 girls (300 per quadrant) would have been needed in the catch-up analysis (Table 2) for the observed difference in insulin resistance (corrected for current weight) of just 12% between the low-high (catch-up) and high-high groups to be significant with 80% power. Even then, a 12% difference is of dubious clinical significance given the 34% difference in insulin resistance (corrected for current weight) between boys and girls overall. The numbers in the EarlyBird cohort are of the same order as those studied by Bavdekar et al. (16) and considerably greater than those of Crowther et al. (9), Hofman et al. (18), or Cianfarani et al. (19).

Although there may have been no significant correlation between insulin resistance at 5 years and birth weight, there were correlations between insulin resistance and current weight, which was stronger in the girls. BMI correlated less closely with insulin resistance than current weight, although concern has been expressed over the use of BMI in young children, in whom it seems to be conditional on height (20).

Insulin resistance was adduced in these studies from a computer algorithm based originally on euglycemic clamp studies carried out in adults (13) and modified subsequently to accommodate more insulin-specific assays (14). Although the algorithm has been rigorously validated in adults (21), it may not apply to young children, so we retested the correlations using fasting insulin levels alone. The correlations remained unchanged, suggesting that insulin levels alone in children reflect the relationships that we observed between current weight, insulin resistance, and fasting glucose. Indeed, the algorithm for insulin resistance incorporates only two variables—insulin and glucose—so that serum insulin will inevitably track with HOMA-IR provided (crucially) that glucose remains within tight limits. Insulin resistance in girls remained approximately one-third (36%) higher than that of the boys, even after correction for weight, BMI, and height, suggesting, very importantly, that girls at 5 years are intrinsically more insulin resistant than boys. It is of interest in this regard that the first U.K. report of type 2 diabetes in childhood describes eight cases between the ages of 9 and 16 years, all of whom were girls (22). Reports of childhood-onset type 2 diabetes worldwide record the same female predominance.

We went on to examine the role of catch-up growth, and noted modest correlations in both sexes between insulin resistance and weight change from birth to 5 years. This observation has been reported before (9) and was interpreted to mean that the combination of low birth weight followed by high weight velocity (low-high) renders a child particularly susceptible to glucose intolerance. However, the report did not document for comparison the glucose tolerance or insulin resistance of children matched for current weight but of higher birth weight (high-high). This omission was crucial, as we could find no difference in the present study in insulin resistance between the low-high and high-high groups, suggesting that current weight best determines insulin resistance in contemporary U.K. children, in whom the point of arrival in terms of weight seems more important than the point of departure.

Indeed, the number of centiles crossed since birth proved to be merely a co-correlate of weight at 5 years. Those who cross the most SDS (i.e., catch-up most) simply reach the highest weight. Thus, children who gain weight excessively after birth may well move up but cannot reasonably be deemed to catch up in a physiological sense. Although centile crossing is inevitably part of acquiring excess weight, we can find no justification for the concept of catch-up as a process of restoration in children who are of normal weight for dates at birth. It seems crucial to establish, given the low prevalence of low birth weight at term in the industrialized world, whether weight catch-up might simply represent overfeeding and the reported associations between postnatal catch-up, later obesity (9),

cardiovascular disease, and glucose intolerance (8,10) merely the emergence of an overweight population rather than some independent relationship between birth weight and subsequent growth.

Our findings do not exclude the influence of low birth weight in nutritionally less privileged populations where low birth weight is common or indeed the effects of intrauterine growth retardation in contemporary populations (4). They do, however, suggest that low birth weight is no longer responsible for the variation in insulin resistance of modern children in more developed nations. Previous studies linking insulin resistance with birth weight were addressing circumstances that effectively no longer exist. We cannot conclude of today's children, as have others of prewar births, that "the consequences of becoming overweight in childhood are conditioned by growth in utero" (8). Our data, taken with those that have been used to support the Barker hypothesis, are consistent with a gradual replacement over the years of gestational undernutrition with childhood overnutrition as the principal cause of insulin resistance in young people. The message is important, as childhood overnutrition is avoidable and correctable in a way that gestational undernutrition may not be.

ACKNOWLEDGMENTS

We are grateful to Roche Products, Smith's Charity (London), The Child Growth Foundation, Eli Lilly, and the London Law Trust for generous support of the EarlyBird Study; to Jenny Perkins for technical help; to Barbara Clewlow for phlebotomy; and to the staff of Children's Day Beds at Derriford Hospital, Plymouth, for accommodating the study.

REFERENCES

1. Kahn BB: Type 2 diabetes mellitus: when insulin secretion fails to compensate for insulin resistance. *Cell* 92:593-596, 1998
2. Reaven GM: Banting lecture 1988. Role of insulin resistance in human disease. *Diabetes* 37:1595-1607, 1988
3. Chukwuma C, Tuomilehto J: The 'thrifty' hypotheses: clinical and epidemiological significance for non-insulin-dependent diabetes mellitus and cardiovascular disease risk factors. *J Cardiovasc Risk* 5:11-23, 1998
4. Calle EE, Thun MJ, Petrelli JM, Rodriguez C, Heath CW: Body-mass index and mortality in a prospective cohort of U.S. adults. *N Engl J Med* 341:1097-1105, 1999
5. Neel JV: Diabetes mellitus: a 'thrifty genotype' rendered detrimental by 'progress.' *Am J Hum Genet* 14:353-362, 1962
6. Barker DJP, Winter PD, Osmond C, Margetts B, Simmonds SJ: Weight in infancy and death from ischaemic heart disease. *Lancet* 2:577-580, 1989
7. Hattersley AT, Tooke JE: The fetal insulin hypothesis: an alternative explanation of the association of low birth weight with diabetes and vascular disease. *Lancet* 353:1789-1792, 1999
8. Eriksson JG, Forsen T, Tuomilehto J, Winter PD, Osmond C, Barker DJ: Catch-up growth in childhood and death from coronary heart disease: longitudinal study. *Br Med J* 318:427-431, 1999
9. Crowther NJ, Cameron N, Trusler J, Gray IP: Association between poor glucose tolerance and rapid post-natal weight gain in seven-year-old children. *Diabetologia* 41:1163-1167, 1998
10. Ong KL, Ahmed ML, Emmett M, Preece MA, Dunger D: Association between post-natal catch-up growth and obesity in childhood: prospective cohort study. *Br Med J* 320:967-971, 2000
11. Lucas A, Fewtrell MS, Cole TJ: Fetal origins of adult disease: the hypothesis revisited. *Br Med J* 319:245-249, 1999
12. *Progress Towards Health for All. Statistics of Member States.* Geneva, World Health Organization, 1994, p. 26-35
13. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC: Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 28:412-419, 1985
14. Levy JC, Matthews DR, Hermans MP: Correct homeostasis model assessment (HOMA) evaluation uses the computer program. *Diabetes Care* 21:2191-2192, 1998
15. Prescott-Clark P, Primates P, Eds. *Health Survey for England.* London, HMSO, 1998
16. Bavdekar A, Yajnik CS, Fall CH, Bapat S, Pandit AN, Deshpande V, Bhave S, Kellingray SD, Joglekar C: Insulin resistance syndrome in 8-year-old Indian children: small at birth, big at 8 years, or both? *Diabetes* 48:2422-2429, 1999
17. Hales CN, Barker DJ, Clark PM, Cox LJ, Fall C, Osmond C, Winter PD: Fetal and infant growth and impaired glucose tolerance at age 64. *Br Med J* 303:1019-1022, 1991
18. Hofman PL, Cutfield WS, Robinson EM, Bergman RN, Menon RK, Sperling MA, Gluckman PD: Insulin resistance in short children with intrauterine growth retardation. *J Clin Endocrinol Metab* 82:402-406, 1997
19. Cianfarani S, Germani D, Branca F: Low birthweight and adult insulin resistance: the "catch-up growth" hypothesis. *Arch Dis Child Fetal Neonatal Ed* 81:F71-F73, 1999
20. Mulligan J, Voss LD: Identifying very fat and very thin children: test of criterion standards for screening test. *Br Med J* 319:1103-1104, 1999
21. Bonora E, Kiechl S, Willeit J, Oberhollenzer F, Egger G, Targher G, Alberiche M, Bonadonna R, Muggeo M: Prevalence of insulin resistance in metabolic disorders: the Bruneck study. *Diabetes* 47:1643-1649, 1998
22. Ehtisham S, Barrett TG, Shaw NJ: Type 2 diabetes mellitus in U.K. children: an emerging problem. *Diabet Med* 17:867-871, 2000